sonnel on the battlefield under direct nerve gas attack. To date, the combination of atropine and 2–PAM is still the antidote of choice for cholinesterase inhibitors. However, their usefulness under battlefield conditions is severely limited due to their present cumbersome form, requiring transport of a relatively bulky package consisting of a vial of powder, a vial of diluent and a separate hypodermic syringe, and necessitating precious time for sterile reconstitution under adverse conditions.

It was therefore an objective of this invention to provide a stabilized 2–PAM solution of sufficient concentration to enable ready administration of a therapeutic parenteral dose. It was a further objective of this invention to provide a stabilized 2–PAM solution which could be packaged in any of the currently available disposable syringe devices, thus minimizing package size and eliminating the disadvantage associated with the reconstitutible form described above. Another objective of this invention was to provide a stabilized concentrated solution of 2–PAM which could be used with any of the currently available autoinjector devices, to enable military personnel to administer a therapeutic parenteral dose to themselves immediately upon being exposed to nerve gases. It was a final objective of this invention to provide a stabilized concentrated 2–PAM solution containing a therapeutic dose of atropine for single parenteral administration of both life saving antidotes.

I have found that all of these objectives can be attained with the practice of my invention for stabilizing concentrated 2–PAM solutions, which I shall now describe.

I have found that aqueous 2–PAM solutions at concentrations greater than 10% w./v., and ranging to the aqueous solubility of the particular salt at the temperature used, can be stabilized by the addition of an inorganic acid such as hydrochloric acid, nitric acid, sulfuric acid or perchloric acid, the amount of acid required being dependent upon the concentration of 2–PAM desired in solution and sufficient to adjust the pH of the solution to one within the range 1.0 to 3.0. For example, I have prepared a solution of 2–PAM chloride containing 330 mg. of the salt per ml. of solution, the pH of the solution being adjusted to 1.3 by the addition of hydrochloric acid. I have stored this solution for one year at 45° C. (113° F.) and have found 98% of the 2–PAM content after this grossly accelerated storage condition. In contradistinction to this finding is the reported chemical half-life for 0.1% 2–PAM solution at pH 1.3 of 10 days at 37° C.

This solution has been injected intramuscularly into rabbits and the injection site has been examined histologically and compared to that from the presently marketed reconstituted powder form. No differences were observed in this testing.

I have also found that this same stability result at 33% w./v. concentration can be obtained using the nitrate, hydrogensulfate, fumarate, lactate, tartrate or methane sulfonate salt of 2–PAM, and is independent of the inorganic acid used to adjust the pH as long as solubility is not affected. For example, sulfuric and perchloric acids have similarly been employed to obtain the desired pH and essentially identical stability.

Furthermore, I have found that atropine sulfate at a concentration up to 5 mg./ml. can be added to all of these solutions without affecting the stability of the 2–PAM. I have also found that the atropine in these solutions at pH 1.3 is relatively unstable at 45° C., having a chemical half-life of less than one year. However, I have been able to prepare combination solutions of 2–PAM chloride (330 mg./ml.) and atropine sulfate (2 mg./ml.) with the pH adjusted to 2.0 with any of the inorganic acids listed above. These solutions exhibit negligible loss of 2–PAM after one year storage at 25° C. and approximately 5% loss of 2–PAM after one year at 37° C. While the atropine loss from these solutions was more rapid than the 2–PAM, 3% in one year at 25° C. and 7% in one year at 37° C., these solutions can be considered to possess adequate stability for three years at 25° C. Shelf-life may be extended by the incorporation of an overage of either or both of the antidotal agents.

In the practice of my invention I prefer to use 2–PAM chloride as the soluble form for preparing the solution. As the inorganic acid stabilizer I prefer to use hydrochloric acid. For the combination antidotal solution composed of 2–PAM and atropine I prefer to use atropine sulfate as the source of soluble atropine.

The following specific examples will serve to illustrate the extent of this invention and should not be considered as limiting it in any way.

EXAMPLE 1

2–PAM chloride—33.3 gm.
Hydrochloric acid 1.0 N q.s. to pH 1.3
Water for injection U.S.P. q.s.—100.0 ml.

The 2–PAM chloride is dissolved in about 90 ml. of water for injection. The pH is adjusted to pH 1.3 with 1.0 N hydrochloric acid. The volume is brought up to 100 ml. with water for injection. The solution is sterilized by filtration through a Millipore® filter using the HA pad with prefilter disc.

The stability of this solution was determined in 20 ml. Pyrex glass ampules and 20 ml. Type I clear glass vials sealed with FI 68 gray butyl (West 860) closures.

The following stability data were obtained after 1 year, expressed as percent 2–PAM chloride remaining.

45° C.:	
Ampules	96
Vials	96.5
37° C.:	
Ampules	100
Vials	99.9
25° C.:	
Ampules	100
Vials	100

EXAMPLE 2

2–PAM methane sulfonate—25 gm.
Sulfuric acid, U.S.P. 1.0 N q.s. to pH 1.5
Water for injection, U.S.P. q.s.—100 ml.

The procedure used to prepare the solution is similar to that described in Example I except the pH was adjusted to 1.5 with 1.0 N sulfuric acid.

The following results were obtained after 1 year, expressed as percent remaining.

45° C.:	
Ampules	98
Vials	98.2
37° C.:	
Ampules	100
Vials	99.8
25° C.:	
Ampules	100
Vials	100

EXAMPLE 3

2–PAM chloride—10 gm.
Atropine sulfate, U.S.P.—0.30 gm.
Perchloric acid, U.S.P. 1.0 M q.s. to pH 2.0
Water for injection U.S.P. q.s.—100 ml.

The procedure used to prepare the above solution is similar to that described in Example 1 except the 2–PAM chloride and atropine sulfate are dissolved in 90 ml. of water and the pH is adjusted with 1.0 M perchloric acid.

The following stability results were obtained expressed as percent remaining after 1 year.